CLAIMS

1. A process for the purification of olanzapine characterised in that said process comprises the following steps:
   a) mixing olanzapine with an organic acid in an organic solvent or a mixture of organic solvents to form an olanzapine acid addition salt,
   b) precipitating and isolating the olanzapine acid addition salt and,
   c) transformation of the olanzapine acid addition salt to olanzapine.

2. The process according to claim 1 wherein the organic acid in step (a) is selected from the group consisting of sulfonic acids or carboxylic acid.

3. The process according to claim 2 wherein the carboxylic acid is selected from the group consisting of fumaric acid and benzoic acid.

4. The process according to claim 1 wherein the organic solvent in step (a) is selected from the group consisting of tetrahydrofurane, acetone, dimethylformamide and acetonitrile.

5. The process according to claim 1 wherein the mixture of organic solvents in step (a) is a mixture of tetrahydrofurane with at least one polar solvent.

6. The process according to claim 5 wherein said polar solvent is selected from the group consisting of dimethylformamide, dimethylacetamide, N-methylpyrrolidone, 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone, 1,3-dimethyl-2-imidazolidinone, tetramethylurea, dimethyl sulfoxide, sulfolane, acetone and acetonitrile.

7. The process according to claim 1 characterized in that step (c) comprises the following substeps:
   i) dissolving an acid addition salt of olanzapine in water,
   ii) adjusting pH of the obtained solution to about 8-10,
   iii) extracting olanzapine from the water phase to the organic solvent phase and

iv) isolating the acid addition salt of olanzapine from the organic solvent phase by concentrating the solution and separation of the crystals.

8. A process for the synthesis of N-desmethylolanzapine from 4-amino-2-methyl-10*H*-thieno[2,3-b][1,5]benzodiazepine and piperazine, characterised in that said synthesis is carried out in a solvent or in a mixture of solvents comprising at least one aliphatic alcohol having a higher boiling point.

9. The process for the synthesis of N-desmethylolanzapine according to claim 8 wherein said solvent comprises *n*-butanol.

10. The process for the synthesis of N-desmethylolanzapine according to claim 8 wherein said mixture of solvents comprises *n*-butanol and at least one aromatic hydrocarbon having a higher boiling point.

11. The process for the synthesis of N-desmethylolanzapine according to claim 8 wherein said aromatic hydrocarbon having a higher boiling point is xylene and/or toluene.

12. The process for the synthesis of N-desmethylolanzapine according to claim 8 wherein piperazine is added in excess with respect to 4-amino-2-methyl-10*H*-thieno[2,3-b][1,5]benzodiazepine.

13. The process for the synthesis of N-desmethylolanzapine according to claim 8 wherein an additional inorganic or organic base is added to the reaction mixture.

14. The process for the synthesis of N-desmethylolanzapine according to claims 8 to 13 characterised in that said process is followed by the precipitation of N-desmethylolanzapine with warm water and washing with esters.

15. The process for the synthesis of N-desmethylolanzapine according to claim 14 wherein said esters are selected from the group consisting of ethyl acetate, propyl acetate and butyl acetate.

16. A process for the preparation of 2-methyl-4-(4-methyl-1-piperazinyl)-10*H*-thieno[2,3-*b*][1,5]benzodiazepine (i.e. olanzapine) of light colour without dark brown or green tinges characterised in that said process comprises the N-methylation of N-desmethylolanzapine with a methylating agent in an organic solvent or in a mixture of organic solvents.

17. The process for the preparation of olanzapine according to claim 16 wherein N-desmethylolanzapine is prepared according to a process as disclosed in claims 8 to 15.

18. The process for the preparation of olanzapine according to claim 16 wherein said process further comprises a purification step of olanzapine as disclosed in claims 1 to 7.

19. A process for the preparation of olanzapine in the form of an acid addition salt characterized in that said process comprises the steps of:
    a) mixing olanzapine with an organic acid in a solvent or a mixture of solvents and
    b) precipitating and isolating the olanzapine acid addition salt by separation of crystals.

20. The process according to claim 19 wherein said organic acid is selected from the group consisting of benzoic acid and sulfonic acids.

21. The process according to claim 19 wherein said organic solvent, mixture of organic solvents and polar solvent correspond respectively to the same disclosed in claims 4, 5 and 6 respectively.

22. A process for the preparation of olanzapine in the form of an acid addition salt characterized in that said process comprises the following steps:
    a) 4-amino-2-methyl-10H-thieno[2,3-b][1,5]benzodiazepine hydrochloride is reacted with N-methylpiperazine to yield olanzapine and
    b) the obtained olanzapine is transformed to an acid addition salt thereof.

23. The process according to claim 22 characterized in that step (b) comprises the following substeps:

i) the obtained reaction mixture is diluted with water,

ii) the diluted reaction mixture is extracted with an organic solvent,

iii) the organic phase is evaporated and the residue is diluted with a second solvent to obtain a solution,

iv) an organic acid is added to the solution to precipitate olanzapine acid addition salt and

v) precipitated olanzapine acid addition salt is isolated by separation of crystals.

24. A process for the preparation of olanzapine in the form of an acid addition salt characterized in that said process comprises the following steps:

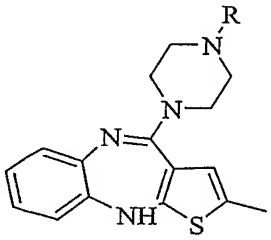
a) N-desmethylolanzapine is reacted with a methylating agent to yield olanzapine,

b) the obtained reaction mixture is diluted with water and acidified with an acid,

c) to the reaction mixture, an organic solvent is added and the phases are separated,

d) the obtained water phase is neutralized and olanzapine is extracted with an organic solvent to obtain the organic solvent phase and

e) an organic acid or substituted organic acid or an organic acid derivative of formula RX; wherein R represents an organic radical such as acetyl, propionyl, chloroacetyl and X is selected from a group of Cl, Br or I; or an organic acid anhydride; is added to the organic phase to form a N-substituted N-desmethylolanzapine derivative of formula 2



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f) the obtained organic solvent phase is optionally evaporated and the residue is diluted with a second organic solvent,

g) an organic acid is added either to the obtained diluted solution or directly to the olanzapine extract from said extraction in step (d) and

h) precipitated olanzapine acid addition salt is isolated by separation of the crystals.

25. The process according to claim 24 wherein the organic solvent in steps (c) and (d) is a chlorinated solvent.

26. The process according to claim 25 wherein said chlorinated solvent is methylene chloride.

27. The process according to claim 24 wherein the organic solvent in steps (c) and (d) is methylene chloride and said second solvent in step (f) is methanol.

28. The process for the preparation of olanzapine acid addition salt according to claims 19-27 characterized in that it comprises a subsequent treatment of remaining solution obtained from isolation of final olanzapine with an organic acid.

29. A process for the preparation of olanzapine, preferably in a crystalline form, characterized in that it is prepared from an olanzapine acid addition salt by recovering olanzapine from the said salt.

30. The process for the preparation of olanzapine from an acid addition salt thereof according to claim 29 characterized in that it comprises the substeps as described in claim 1.

31. The process for the preparation of olanzapine crystal form I from an acid addition salt thereof according to claims 29-30 wherein the crystals are isolated from an organic solvent.

32. The process for the preparation of olanzapine crystal form II from an acid addition salt thereof according to claims 29-30 wherein the crystals are isolated from one or more organic solvents.

33. A process for the preparation of olanzapine comprising the following steps:
    a) transformation of 4-amino-2-methyl-10*H*-thieno[2,3-b][1,5]-benzodiazepine hydrochloride to 2-methyl-4-(1-piperazinyl)-10*H*-thieno-[2,3-*b*][1,5]benzo-diazepine,
    b) transformation of 2-methyl-4-(1-piperazinyl)-10*H*-thieno[2,3- *b*][1,5]benzo-diazepine to crude olanzapine,
    c) transformation of crude olanzapine to an acid addition salt thereof and
    d) transformation of an acid addition salt of olanzapine to olanzapine.

34. The process for the preparation of a derivative of N-desmethylolanzapine of formula 2 as defined in claim 24 comprising the addition of an organic acid derivative, defined as RX as defined in claim 24 or an organic acid anhydride, to N-desmethylolanzapine.

35. Olanzapine prepared according to any of the previous processes disclosed in the claims 1-7 and 29-33 characterized in that N-desmethylolanzapine content in the final product of olanzapine is less than 0.1 %.

36. Olanzapine prepared according to any of the previous processes disclosed in the claims 1-7, 16-18 and 29-33 that contains less than 0.05 % of piperazine 1,4-bis-4-yl-(2-methyl)-10H-thieno-[2,3-b][1,5]benzodiazepine.

37. Olanzapine in a form of an acid addition salt with organic acid selected from the group consisting of benzoic and sulfonic acids.

38. Benzoic acid addition salt of 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine.

39. A pharmaceutical formulation comprising olanzapine and at least one pharmaceutically acceptable ingredient characterised in that olanzapine has been prepared by the processes according to claims 1-7, 16-18 or 29-33.

40. Use of organic acids in a process of preparation of olanzapine wherein olanzapine is purified via the formation of an acid addition salt.

41. Use of olanzapine prepared by a process according to claims 1-7, 16-18 or 29-33 for the preparation of a medicament for the treatment of mental diseases and conditions.

42. Use of olanzapine prepared by a process according to claims 1-7, 16-18 or 29-33 for the preparation of a pharmaceutical formulation together with at least one pharmaceutically acceptable ingredient.

43. Method of treating mental diseases and conditions such as disorders of the central nervous system, schizophrenia, hallucination, acute mania, depression, and the like which comprises administering a therapeutically effective amount of olanzapine prepared by the processes according to claims 1-7, 16-18 or 29-33 in conjunction with a pharmaceutically acceptable diluent or carrier.